

STATISTICAL EVALUATION AND REVIEW

Date: July 20, 1998
Type: BLA
FDA Number: 97-1325
Product/Application: ONTAK (denileukin **difitox** injection)
Sponsor: Seragen Inc.
Indication: For the treatment of patients with cutaneous T-cell lymphoma (CTCL) which is persistent or recurrent despite prior therapy.
Title of Document: Original biological license application
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Background

ONTAK is a novel fusion protein designed to direct the cytocidal action of diphtheria toxin, in a site-specific manner, to malignant cells which express the IL-2R. Cells expressing the IL-2R are found in clinical specimens of certain leukemias and lymphomas including mycosis fungoides and Sezary syndrome, the most common forms of cutaneous T-cell lymphoma (CTCL).

This submission is based primarily on two completed clinical studies. The clinical data were supplied for these two studies and two incomplete studies on a CD-ROM. This report will examine the two completed clinical studies, **P401** and **P410**. Simplified efficacy **dataset** for these two studies were received on disk on April 15, 1998.

P401 is a dose ranging (3 to 31 **mcg/kg/d**) study with 73 CTCL, non-Hodgkins lymphoma (NHL), and Hodgkins disease (HD) patients. The study drug was administered as a short intravenous infusion daily for 5 consecutive days per course, with subsequent courses every 3 weeks.

P410 evaluated two doses (9 **mcg/kg/day**, 18 **mcg/kg/d**) of ONTAK in 71 CTCL patients. This was a randomized, double-blind, two-arm study in patients with disease stage Ib to **IVa**. Study drug administration was similar to study **P401**. Demographic and medical characteristics of the patients in the two studies is provided below.

Table 1. Demographic characteristics.

		P410 (n=73)	P410 (n=71)	Total
Sex	Male	44 (60.3%)	37 (52.1%)	81
	Female	29 (39.7%)	34 (47.9%)	63
Race	Caucasian	32 (43.8%)	53 (74.7%)	85
	Black	7 (9.6%)	12 (16.9%)	19
	Other	34 ()	6 ()	40
Age	Mean \pm SD	50.7 \pm 18.4	60.8 \pm 14.2	
Weight	Mean \pm SD	75.6 \pm 18.2	79.3 \pm 17.7	

Table 2. Medical Characteristics

		P410 (n=73)	P410 (n=71)	Total
Prior Therapies	≤ 3	29 (39.7%)	9 (12.7%)	38
	≥ 4	44 (60.3%)	62 (87.3%)	106
CTCL Stage	Ia	2 (5.7%)	0 (0.0%)	2
	Ib	6 (17.1%)	16 (22.5%)	22
	IIa	4 (11.4%)	10 (14.1%)	14
	IIb	6 (17.1%)	19 (26.8%)	25
	III	7 (20.0%)	11 (15.5%)	18
	IVa	9 (25.7%)	15 (21.1%)	24
	Ivb	1 (2.9%)	0 (0.0%)	1
Diagnosis	CTCL	35 (48.0%)	71 (100.0%)	106
	HD	21 (28.8%)	0 (0.0%)	21
	NHL	17 (23.3%)	0 (0.0%)	21

As noted earlier, P401 employed treatment doses from 6 mcg/kg/d to 31 mcg/kg/d and enrolled from 3 patients in the lowest dose group to a maximum of 18 patients in the 19 mcg/kg/d dose group. There were only 35 patients in the study with CTCL. Study P410 was entirely in CTCL patients. Demographic and medical characteristics of patients and the response rates are provided in the tables on next several pages. Study P401 was primarily a dose ranging study and therefore no statistical tests are provided. These results are provided from pages 3 to 7. Beginning page 8, results of the study P410 are provided. This compares the two doses of the treatment. Most of the analyses show no significant difference in the two doses.

STUDY = P401

WEIGHT (kg) By DOSE ADMINISTERED

Means and Std Deviations				
Dose	Number	Mean	Std Dev	Std Err Mean
6	2	66.0000	2.1213	1.500
9	6	75.9333	22.8137	9.314
12	3	82.8333	33.0579	19.086
15	3	85.2333	23.8215	13.753
19	a	76.0500	15.7394	5.565
23	6	77.2333	15.3144	6.252
27	3	73.5000	15.3216	8.846
31	4	93.5500	23.5436	11.772

TOTAL # DOSES By DOSE ADMINISTERED

Means and Std Deviations				
Dose	Number	Mean	Std Dev	Std Err Mean
6	2	22.00	24.04	17.00
9	6	16.50	14.38	5.87
12	3	26.67	12.58	7.27
15	3	1a.33	18.93	10.93
19	a	20.13	1 2.28	4.34
23	6	22.33	8.41	3.43
27	3	23.00	7.21	4.16
31	4	6.75	5.68	2.84

TOTAL NUMBER OF COURSES By DOSE ADMINISTERED

Means and Std Deviations				
Dose	Number	Mean	Std Dev	Std Err Mean
6	2	4.50	4.95	3.50
9	6	3.50	2.88	1.18
12	3	5.33	2.52	1.45
15	3	3.67	3.79	2.19
19	a	4.13	2.42	0.85
23	6	4.50	1.64	0.67
27	3	4.67	1.53	0.88
31	4	1.50	1.00	0.50

AGE By DOSE ADMINISTERED

Means and Std Deviations				
Dose	Number	Mean	Std Dev	Std Err Mean
6	2	67.00	9.90	7.00
9	6	57.33	13.11	5.35
12	3	57.67	19.14	11.05
15	3	58.33	14.57	8.41
19	a	62.63	11.06	3.91
23	6	60.17	17.66	7.21
27	3	-67.33	2.52	1.45
31	4	64.50	16.74	a.37

DISEASE DURATION (yrs) By DOSE ADMINISTERED

Dose	Means and Std Deviations		Std Dev	Std Err	Mean
	Number	Mean			
6	2	2.10	0.62		0.44
9	6	2.69	2.42		0.99
12	3	4.83	5.97		3.45
15	3	3.46	0.96		0.55
19	8	2.84	2.45		0.87
23	6	5.66	4.35		1.78
27	2	3.57	4.70		3.32
31	3	2.80	1.96		1.13

TABLE OF RACE BY DOSE

RACE DOSE ADMINISTERED

Frequency	6	9	12	15	19	23	27	31	Total
UNK	0	1	0	1	2	0	1	0	5
CAUCASIAN	0	3	3	1	3	5	2	2	19
SLACK	0	2	0	0	2	1	0	1	6
OTHER	2	0	0	1	1	0	0	1	5
Total	2	6	3	3	8	6	3	4	35

TABLE OF SEX BY DOSE

SEX DOSE ADMINISTERED

Frequency	6	9	12	15	19	23	27	31	Total
MALE	1	3	1	2	6	5	2	4	24
FEMALE	1	3	2	1	2	1	1	0	11
Total	2	6	3	3	6	6	3	4	35

TABLE OF STAGE BY DOSE

CTCL STAGE DOSE ADMINISTERED

Frequency	6	9	12	15	19	23	27	31	Total
Ia	0	0	1	0	1	0	0	0	2
Ib	0	1	1	0	0	2	1	1	6
IIa	0	1	0	0	2	0	0	1	4
IIb	1	0	1	0	0	1	2	1	6
III	1	1	0	2	2	1	0	0	7
IVa	0	2	0	1	3	2	0	1	9
IVb	0	1	0	0	0	0	0	0	1
Total	2	6	3	3	8	6	3	4	36

TABLE OF REASON OFF STUDY BY DOSE

REASON OFF STUDY	DOSE ADMINISTERED				Total
Frequency	6	9	12	15	
COMPLETED	1	2	1	1	12
AE	0	2	0	0	8
PT SELF-WITHDRAW	0	0	1	0	1
PROG DISEASE	1	2	1	2	13
OTHER	0	0	0	0	1
Total	2	6	3	3	35

TABLE OF REASON OFF STUDY BY DOSE

REASON OFF STUDY	DOSE ADMINISTERED				Total
Frequency	19	23	27	31	
COMPLETED	3	3	1	0	12
AE	2	0	1	3	8
PT SELF-WITHDRAW	0	0	0	0	1
PROG DISEASE	2	3	1	1	13
OTHER	1	0	0	0	1
Total	8	6	3	4	35

TABLE OF RESPSTAT BY DOSE

RESPONSE STATUS	DOSE ADMINISTERED				
Frequency	6	9	12	15	Total
NOT APPLICABLE	1	5	0	2	22
RELAPSE	1	1	2	1	9
LOST TO FOLLOW-UP	0	0	1	0	4
Total	2	6	3	3	35

TABLE OF RESPSTAT BY DOSE

RESPONSE STATUS	DOSE ADMINISTERED				
Frequency	19	23	27	31	Total
NOT APPLICABLE	5	5	0	4	22
RELAPSE	2	0	2	0	9
LOST TO FOLLOW-UP	1	1	1	0	4
Total	8	6	3	4	35

TABLE OF NUMBER OF PRIOR THERAPIES BY DOSE

NUMBER OF PRIOR THERAPIES	DOSE ADMINISTERED								
Frequency	6	9	12	15	19	23	27	31	Total
<=3	1	3	2	2	6	2	2	2	20
>=4	1	3	1	1	2	4	1	2	15
Total	2	6	3	3	8	6	3	4	35

TABLE OF BEST RESPONSE BY DOSE

BEST RESPONSE	DOSE ADMINISTERED								
Frequency	6	9	12	15	19	23	27	31	Total
CR	0	0	1	1	1	1	1	0	5
PD	1	1	0	1	0	1	0	0	4
PR	1	1	2	0	2	0	2	0	6
SD	0	4	0	1	5	4	0	1	15
Total	2	6	3	3	8	6	3	1	32

TABLE OF DISEASE STAGE BY RESPONSE STATUS

CTCL STAGE	RESPONSE STATUS			Total
	NOT APPLICABLE	RELAPSE	LOST TO FOLLOW-UP	
Ia	0	0	2	2
Ib	3	2	1	6
IIa	2	2	0	4
IIb	2	3	1	6
III	5	2	0	7
IVa	9	0	0	9
IVb	1	0	0	1
Total	22	9	4	35

TABLE OF STAGE BY BESTRESP

CTCL STAGE		BEST RESPONSE				
Frequency	CR	PD	PA	SD	Total	
Ia	2	0	0	0	2	
Ib	1	1	2	1	5	
IIa	0	0	2	1	3	
IIb	1	0	3	1	5	
III	1	2	1	3	7	
IVa	0	1	0	8	9	
IVb	0	0	0	1	1	
Total	5	4	8	15	32	

Frequency Missing = 3

RESULTS OF STUDY P410**WEIGHT (KG)****QUINTILES**

dose	minimum	10.0%	25.0%	median	75.0%	90.0%	maximum
9	47.5	56.3	67.3	78.7	92.1	104.4	134.3
18	53.6	57.1	62.9	77.6	93.2	98.1	122.5

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err	Mean
9	35	80.9	18.8		3.2
18	36	77.7	16.7		2.8

Difference = 3.12 p = 0.46 95% CI = (-5.30, 11.54) Wilcoxon Test: **p=0.53**

TOTAL # COURSES By DOSE ADMINISTERED**Quantiles**

dose	minimum	10.0%	25.0%	median	75.0%	90.0%	maximum
9	1	1	2	6	8	8.4	10
18	1	1	1.25	6	8	10	11

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err	Mean
9	35	5.3	3.0		0.51
18	36	5.1	3.5		0.58

Difference = 0.18 p = 0.82 95% CI = (-1.36, 1.71) Wilcoxon Test: **p=0.67**

TOTAL # DOSES By DOSE ADMINISTERED**Quantiles**

dose	minimum	10.0%	25.0%	median	75.0%	90.0%	maximum
9	1	4.6	9	30	38	40.4	50
18	1	5	5.25	28	40	45.3	53

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err	Mean
9	35	24.51	15.28		2.58
18	36	24.31	16.86		2.81

Difference = 0.208 p = **0.9566** 95% CI = (-7.42, 7.83) Wilcoxon Test: **p=0.97**

AGE By DOSE ADMINISTERED**Quantiles**

dose	minimum	10.0%	25.0%	median	75.0%	90.0%	maximum
9	36	37.6	47	64	72	78.8	91
18	26	40.4	50.25	65.5	71	75.3	78

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err	Mean
9	35	-60.82	15.34		2.59
18	36	60.86	13.30		2.22

Difference = -0.0325 p = 0.9924 95% CI = (-6.82, 6.76) Wilcoxon Test: **p=0.77**

DISEASE	DURATION (yrs)	By	DOSE	ADMINISTERED
1. Measles	1-2	100%	100%	100%
2. Mumps	1-2	100%	100%	100%
3. Rubella	1-2	100%	100%	100%
4. Polio	1-2	100%	100%	100%
5. Tetanus	1-2	100%	100%	100%
6. Diphtheria	1-2	100%	100%	100%
7. Pertussis	1-2	100%	100%	100%
8. Hib	1-2	100%	100%	100%
9. Pneumococcus	1-2	100%	100%	100%
10. Meningitis	1-2	100%	100%	100%
11. Hepatitis A	1-2	100%	100%	100%
12. Hepatitis B	1-2	100%	100%	100%
13. HIV	1-2	100%	100%	100%
14. Tuberculosis	1-2	100%	100%	100%
15. Syphilis	1-2	100%	100%	100%
16. Gonorrhea	1-2	100%	100%	100%
17. Chlamydia	1-2	100%	100%	100%
18. Herpes	1-2	100%	100%	100%
19. HIV	1-2	100%	100%	100%
20. AIDS	1-2	100%	100%	100%

		Quantiles					
dose	minimum	10.0%	25.0%	median	75.0%	90.0%	maximum
9	0.88	1.29	2.01	5.08	8.57	11.91	15.41
18	0.31	1.053	2.82	4.74	9.89	12.47	20.34

Means and Std Deviations					
Level	Number	Mean	Std Dev	Std Err	Mean
9	34	5.76	4.03		0.69
18	36	6.05	4.57		0.76

Difference = -0.30 p = **0.77** 95% CI = (-2.36, 1.76) **Wilcoxon Test: p=0.93**

AQUAPHOR % CHANGE FROM BASELINE By DOSE ADMINISTERED

	Quantiles						
dose	minimum	10.0%	25.0%	median	75.0%	90.0%	maximum
9	-100	-100	-100	0	14.56	256.25	600
18	-100	-100	-100	0	100	146.67	325

Means and Std Deviations				
Level	Number	Mean	Std Dev	Std Err Mean
9	30	26.04	171.10	31.24
18	31	3.31	109.75	19.71

Difference = 22.73 p = **0.54** 95% CI = (-50.67, 96.13) **Wilcoxon Test: p=0.89**

EUCERIN® % CHANGE FROM BASELINE By DOSE ADMINISTERED

		Quantiles					
dose	minimum	10.0%	25.0%	median	75.0%	90.0%	maximum
9	-100	-100	-6.25	0	67.22	335	400
18	-100	-100	-100	0	90.625	195	400

Means and Std Deviations				
Level	Number	Mean	Std Dev	Std Err Mean
9	30	38.52	132.13	24.12
18	30	15.42	120.51	22.00

Difference = 23.10 p = **0.48** 95% CI = (-42.25, 88.46) Wilcoxon Test: p = **0.46**

% CHANGE PRURITUS VISUAL ANALOG SCALE By DOSE ADMINISTERED

dose	Quantiles						
	minimum	10.0%	25.0%	median	75.0%	90.0%	maximum
9	-100	-99.55	-96.68	48.33	-9.01	59.48	188.89
18	-100	-100	-88.26	-52.17	-12.50	51.45	413.33

Means and Std Deviations						
Level	Number	Mean	Std Dev	Std Err	Mean	
9	33	-38.15	65.67		11.43	
18	33	-33.13	94.93		16.53	

Difference = -5.013 p =0.80 95% CI = (45.16, 35.13) Wilcoxon Test: p=0.83

% CHANGE PHYSICIAN'S GLOBAL ASSESSMENT By DOSE ADMINISTERED

dose	Quantiles						
	minimum	10.0%	25.0%	median	75.0%	90.0%	maximum
9	-100	-97	-73.68	-50	-18.33	-2.22	44
18	-100	-100	-87.63	-57.88	-16.46	15.44	32.43

Means and Std Deviations						
Level	Number	Mean	Std Dev	Std Err	Mean	
9	35	-46.56	35.27		5.96	
18	34	-50.65	40.58		6.96	

Difference = 4.09 p = 0.66 95% CI = (-14.16, 22.34) Wilcoxon Test: p=0.54

CALCULATED % RESPONSE VALUE By DOSE ADMINISTERED

dose	Quantiles						
	minimum	10.0%	25.0%	median	75.0%	90.0%	maximum
9	-100	-100	-78.925	-58.025	-27.425	7.15	33.6
18	-100	-100	-81.8	-67.2	-31.45	20.54	59.9

Means and Std Deviations						
Level	Number	Mean	Std Dev	Std Err	Mean	
9	34	-52.23	37.76		6.48	
18	33	-54.58	41.87		7.29	

Difference = 2.34 p = 0.81 95% CI = (-17.10, 21.79) Wilcoxon Test: p=0.51

DURATION FROM FIRST DOSE (MONTHS) By DOSE ADMINISTERED

dose	Quantiles						
	minimum	10.0%	25.0%	median	75.0%	90.0%	maximum
9	0.46	0.80	2.56	3.94	5.78	6.81	12.48
18	0.69	0.85	1.43	4.63	6.51	7.82	12.94

Means and Std Deviations					
Level	Number	Mean	Std Dev	Std Err	Mean
9	3 5	4.18	2.65		0.45
18	3 3	4.41	3.14		0.55

Difference = -0.23 p = 0.75 95% CI = (-1.63, 1.18) **Wilcoxon Test: p=0.69**

DURATION FROM FIRST RESPONSE By DOSE ADMINISTERED

dose	Quantiles						
	minimum	10.0%	25.0%	median	75.0%	90.0%	maximum
9	0.46	0.97	1.84	3.91	5.62	6.74	11.07
18	0.69	0.88	1.41	2.53	5.11	7.04	11.53

Means and Std Deviations					
Level	Number	Mean	Std Dev	Std Err	Mean
9	3 5	3.89	2.40		0.41
18	3 3	3.50	2.71		0.47

Difference = 0.39 p = 0.53 95% CI = (-0.84, 1.63) **Wilcoxon Test: p=0.34**

Study = P410

TABLE OF RACE BY DOSE

RACE	DOSE ADMINISTERED		
Frequency	9	18	Total
CAUCASIAN	28	25	53
BLACK	5	7	12
OTHER	2	4	6
Total	35	36	71

TABLE OF SEX BY DOSE

SEX	DOSE ADMINISTERED		
Frequency1	9	18	Total
MALE	20	17	37
FEMALE	15	19	34
Total	35	36	71

TABLE OF STAGE BY DOSE

CTCL STAGE	DOSE ADMINISTERED		
Frequency	9	18	Total
Ib	7	9	16
IIa	7	3	10
IIb	9	10	19
III	5	6	11
IVa	7	8	15
Total	35	36	71

TABLE OF **DOCUMENTED** RESPONSE BY DOSE

DOCUMENTED RESPONSE

	DOSE ADMINISTERED		
Frequency	9	18	Total
NO	27	23	50
YES (> 6 WK BY D ERC)	8	13	21
Total	35	36	71

Fisher's Exact test: **p=0.30**

TABLE OF REASON OFF STUDY BY DOSE

REASON OFF STUDY DOSE ADMINISTERED

Frequency	9	18	Total
COMPLETED	14	15	29
AE	11	15	26
PT SELF-WITHDRAW	2	3	5
PROT VIOLATION	1	0	1
PROG DISEASE	3	1	4
OTHER	0	1	1
WORSE DISEASE	3	1	4
STILL ACTIVE	1	0	1
Total	35	36	71

TABLE OF RESPONSE STATUS BY DOSE

RESPONSE STATUS DOSE ADMINISTERED

Frequency	9	18	Total
NOT APPLICABLE	27	23	50
RELAPSE	6	6	14
LOST TO FOLLOW-UP	0	1	1
ONGOING	2	4	6
Total	35	36	71

TABLE OF NUMBER OF PRIOR THERAPIES BY DOSE

NUMBER OF PRIOR THERAPIES

Frequency	DOSE ADMINISTERED		Total
	9	18	
<=3	4	5	9
>=4	31	31	62
Total	35	36	71

TABLE OF BEST RESPONSE BY DOSE

BEST RESPONSE

Frequency	DOSE ADMINISTERED		Total
	9	18	
CCR	3	3	6
CR	1	2	3
PD	1	1	2
PR	13	17	30
so	17	10	27
Total	35	33	66

Frequency Missing = 3

TABLE OF CTCL STAGE BY RESPONSE STATUS

CTCL STAGE RESPONSE STATUS

Frequency	NOT APPL ICABLE	RELAPSE	LOST TO FOLLOW-U P	ONGOING	Total
Ib	9	3	0	4	16
IIa	7	3	0	0	10
IIb	13	6	0	0	19
III	9	0	0	2	11
IVa	12	2	1	0	15
Total	50	14	1	6	71

TABLE OF CTCL STAGE BY **BEST** RESPONSE

CTCL STAGE		BEST RESPONSE					
Frequency	CCR	CR	PD	PR	SD	Total	
Ib	2	2	1	6	4	15	
IIa	0	0	0	6	3	9	
IIb	3	1	1	7	6	16	
III	0	0	0	6	5	11	
IVa	1	0	0	5	9	15	
Total	6	3	2	30	27	66	

Frequency Missing = 3

RESULTS BY DOCUMENTED RESPONSE**USE OF RESCUE MEDICATIONS By DOCUMENTED RESPONSE**

NO. OF RESCUE MED	DOCUMENTED RESPONSE (%)		
	NO	YES	Total
0	7 (14.00)	0 (0.00)	7
1	11 (22.00)	4 (19.05)	15
2	5 (10.00)	0 (0.00)	5
3	27 (54.00)	17 (80.95)	44
TOTAL	50	21	71

P-value = 0.0175

AQUAPHOR % CHANGE FROM BASELINE By DOCUMENTED RESPONSE

resp	min	10.0%	25.0%	median	75.0%	90.0%	max
no	-100	-100	-59.52	0	100	243.75	600
yes	-100	-100	-100	-100	0	200	250

Wilcoxon Tests (Rank Sums): p=0.0035

EUCERIN % CHANGE FROM BASELINE By DOCUMENTED RESPONSE

resp	minimum	10.0%	25.0%	median	75.0%	90.0%	maximum
no	-100	-100	-75	0	100	335	400
yes	-100	-100	-60	0	0	100	200

Wilcoxon Tests (Rank Sums): $p=0.3006$

% CHANGE PRURITUS VISUAL ANALOG SCALE By DOCUMENTED RESPONSE

resp	min	10.0%	25.0%	median	75.0%	90.0%	maximum
no	-100	-94.07	-62.30	-25.29	-3.125	88.46	413.33
yes	-100	-100	-100	-95.08	-75.51	-40.22	-28.57

Wilcoxon Tests (Rank Sums): $p < 0.0001$

% CHANGE PHYSICIANS GLOBAL ASSESSMENT By DOCUMENTED RESPONSE

resp	min	10.0%	25.0%	median	75.0%	90.0%	maximum
no	-100	-87.23	-61.43	-35.86	-11.36	16.64	44
yes	-100	-100	-100	-79	-64.22	-47.96	-30.77

Wilcoxon Tests (Rank Sums): $p < 0.0001$

CALCULAED % RESPONSE By DOCUMENTED RESPONSE

resp	min	10.0%	25.0%	median	75.0%	90.0%	maximum
no	-100	-96.36	-67.43	-45.1	-11.55	24.52	59.9
yes	-100	-100	-100	-85	-70.8	-60.28	-60

Wilcoxon Tests (Rank Sums): $p < 0.0001$

DURATION FROM FIRST DOSE (months) By DOCUMENTED RESPONSE

resp	min	10.0%	25.0%	median	75.0%	90.0%	maximum
no	0.46	0.78	1.18	3.06	5.09	5.79	6.74
yes	2.69	3.36	4.98	6.60	7.79	12.32	12.94

Wilcoxon Tests (Rank Sums): $p < 0.0001$

DURATION FROM FIRST RESPONSE (months) By DOCUMENTED RESPONSE

resp	min	10.0%	25.0%	median	75.0%	90.0%	maximum
no	0.50	0.69	1.28	2.76	5.13	6.39	7.13
yes	1.45	1.64	2.07	4.37	6.72	10.70	11.53

Wilcoxon Tests (Rank Sums): $p = 0.0212$

**QUALITY OF LIFE DATA
VISIT NO = 2**

CHANGE IN PHYSICAL WELLBEING By TREATMENT

	Quantiles						
Level	minimum	10.0%	25.0%	median	75.0%	90.0%	maximum
IL2-18kg	-7	-3.4	0	2	8	11.4	13
IL2-9 kg	-8	-2.96667	-2	0	4.458333	8	10

Means and Std Deviations				
Level	Number	Mean	Std Dev	Std Err Mean
IL2-18kg	27	3.36728	5.24059	1.0086
IL2-9 kg	30	1.27222	4.28655	0.7826

Difference = 2.09506 95% CL = (-0.43622 • 4.62634)

t-Test: **p=0.1029**,

Wilcoxon Rank Sum Test: p=0.0924

CHANGE IN SOCIAL/FAMILY By TREATMENT

	Quantiles						
Level	minimum	10.0%	25.0%	median	75.0%	90.0%	maximum
IL2-18kg	-8.16667	-6.62667	-4.66667	-1	1	2.333333	3.5
IL2-9 kg	-18	-7.5	-3.625	-1.16667	1.166667	6.8	14

Means and Std Deviations				
Level	Number	Mean	Std Dev	Std Err Mean
IL2-18kg	27	-1.61543	3.08914	0.5945
IL2-9 kg	30	-1.18889	5.65613	1.0327

Difference = -0.42654 95% CI = (-2.88465 - 2.03157)

t-Test: **p=0.7294**,

Wilcoxon Rank Sum Test: p=0.9489

CHANGE IN REL WITH DOCTOR By TREATMENT

	Quantiles						
Level	minimum	10.0%	25.0%	median	75.0%	90.0%	maximum
IL2-18kg	-1	-1	-0.25	0	0	0	1
IL2-9 kg	-2	-1	0	0	0	1	8

Means and Std Deviations				
Level	Number	Mean	Std Dev	Std Err Mean
IL2-18kg	26	-0.19231	0.49147	0.09638
IL2-9 kg	29	0.137931	1.64152	0.30482

Difference = -0.33024 95% CI = (-1.00194, 0.34146)

t-Test: **p=0.3750**

Wilcoxon Rank Sum Test: p=0.4747

CHANGE IN EMOTIONAL By TREATMENT

Level	Quantiles						maximum
	minimum	10.0%	25.0%	median	75.0%	90.0%	
IL2-18kg	-6	4.3	-2	-1	1.25	3.3	4
IL2-9 kg	-7	-6	-3	0	1	3	4

Means and Std Deviations				
Level	Number	Mean	Std Dev	Std Err Mean
IL2-18kg	26	-0.53846	2.56485	0.50301
IL2-9 kg	29	-0.82759	3.17433	0.58946

Difference = 0.2891295% CI = (-1.28338, 1.86163)

t-Test: p = 0.7138 **Wilcoxon Rank Sum** Test: p = 0.9256

CHANGE IN FUNCTIONAL By TREATMENT

Level	Quantiles						maximum
	minimum	10.0%	25.0%	median	75.0%	90.0%	
IL2-18kg	-6	4.3	0	1	2	3.65	4
IL2-9 kg	-11.6667	-8	-1.5	2	4	6	8

Means and Std Deviations				
Level	Number	Mean	Std Dev	Std Err Mean
IL2-18kg	26	0.480769	2.45960	0.48237
IL2-9 kg	29	0.281609	4.65029	0.86354

Difference = 0.19916 95% CI = (-1.84779, 2.24611)

t-test: p = 0.8460 **Wilcoxon Rank Sum** Test: p = 0.8318

VISIT NO = 3

CHANGE IN PHYSICAL WELLBEING By TREATMENT

Level	Quantiles						maximum
	minimum	10.0%	25.0%	median	75.0%	90.0%	
IL2-18kg	-3.16667	-2.7	-1	0	3	11.5	15
U-9 kg	-6	4.8	-1	1	6	11.6	20

Difference = -0.61303 95% CI = (-3.88021, 2.65415)

Means and Std Deviations				
Level	Number	Mean	Std Dev	Std Err Mean
IL2-18kg	22	1.94697	4.72396	1.0072
IL2-9 kg	25	2.56000	6.18145	1.2363

t-Test: p = 0.7073 Wilcoxon Tests (Rank Sums): p = 0.8219

CHANGE IN SOCIAL/FAMILY By TREATMENT

Level	Quantiles						maximum
	minimum	10.0%	25.0%	median	75.0%	90.0%	
IL2-18kg	-8.5	-7.81667	-2.91667	-1.16667	-0.45	2.233333	4
IL2-9 kg	-19	-5.8	-3	0	3.5	8.7	13

Means and Std Deviations				
Level	Number	Mean	Std Dev	Std Err Mean
IL2-18kg	22	-1.86061	3.16921	0.6757
IL2-9 kg	25	-0.00400	6.18892	1.2378

Difference = -1.85661 95% CI = (4.80725, 1.09404)

t-Test: p = 0.2116 Wilcoxon Tests (Rank Sums): p = 0.2119

CHANGE IN REL WITH DOCTOR By TREATMENT

Level	Quantiles						maximum
	minimum	10.0%	25.0%	median	75.0%	90.0%	
IL2-18kg	-1	-1	0	0	0	1	2
IL2-9 kg	-2	-1	0	0	0.5	2	2

Difference = -0.11238 95% CI = (-0.65432, 0.429561)

Means and Std Deviations				
Level	Number	Mean	Std Dev	Std Err Mean
IL2-18kg	21	0.047619	0.74001	0.16148
IL2-9 kg	25	0.160000	1.02794	0.20559

t-Test: p = 0.6780 Wilcoxon Tests (Rank Sums): p = 0.7850

CHANGE IN EMOTIONAL By TREATMENT

Level	Quantiles						
	minimum	10.0%	25.0%	median	75.0%	90.0%	maximum
IL2-18kg	-9	-4	-3	-1	0	0.8	2
IL2-9 kg	-8	-7	-4	-1	1	3	4

Means and Std Deviations				
Level	Number	Mean	Std Dev	Std Err Mean
IL2-18kg	21	-1.57143	2.29285	0.50034
IL2-9 kg	25	-1.56000	3.39215	0.67843

Difference = -0.01143 95% CI = (-1.76757, 1.74472)

t-Test: p = 0.9896 **Wilcoxon** Tests (Rank Sums): p = 0.8500

CHANGE IN FUNCTIONAL By TREATMENT

Level	Quantiles						
	minimum	10.0%	25.0%	median	75.0%	90.0%	maximum
IL2-18kg	-8	-6.4	-2.5	-1	2	4	7
IL2-9 kg	-10	-8.6	-4.5	-1	1.5	7.4	14

Means and Std Deviations				
Level	Number	Mean	Std Dev	Std Err Mean
IL2-18kg	21	-0.52381	3.58635	0.7826
IL2-9 kg	25	-1.11333	5.39348	1.0787

Difference = 0.58952 95% CI = (-2.19029, 3.36934)

t-Test: p = 0.6712 **Wilcoxon** Tests (Rank Sums): p = 0.4122

VISIT NO = 99

CHANGE IN PHYSICAL WELLBEING By TREATMENT

Level	Quantiles						maximum
	minimum	10.0%	25.0%	median	75.0%	90.0%	
IL2-18kg	-15.1667	-1.3	-1	2.1	6.75	16.2	21
IL2-9 kg	-7	-5.9	-2	1	5.625	11.9	16

Means and Std Deviations				
Level	Number	Mean	Std Dev	Std Err Mean
IL2-18kg	28	3.81667	7.52450	1.4220
IL2-9 kg	32	2.11042	6.35039	1.1226

Difference = 1.70625 95% CI = (-1.87919, 5.29169)

t-Test: p = 0.3448 Wilcoxon Tests (Rank Sums): p = 0.2410

CHANGE IN SOCIAL/FAMILY WELL-BEING By TREATMENT

Level	Quantiles						maximum
	minimum	10.0%	25.0%	median	75.0%	90.0%	
IL2-18kg	-7	-5.35833	-3.5	-1	0.75	2.6	7
IL2-9 kg	-13	-6.96667	-4.16667	-2	1.4	5	14

Means and Std Deviations				
Level	Number	Mean	Std Dev	Std Err Mean
IL2-18kg	28	-1.26012	3.20605	0.60589
IL2-9 kg	31	-1.26398	4.98979	0.89619

Difference = 0.00386 95% CI = (-2.20945, 2.21717)

t-Test: p = 0.9972 Wilcoxon Tests (Rank Sums): p = 0.8197

CHANGE IN RELATIONSHIP WITH DOCTOR By TREATMENT

Level	Quantiles						maximum
	minimum	10.0%	25.0%	median	75.0%	90.0%	
IL2-18kg	-3	-1.2	0	0	0	2	2
IL2-9 kg	-2	-1	-0.75	0	0	0.7	1

Means and Std Deviations				
Level	Number	Mean	Std Dev	Std Err Mean
IL2-18kg	27	0.037037	1.05544	0.20312
IL2-9 kg	32	-0.21875	0.70639	0.12487

Difference = 0.255787 95% CI = (-0.20621, 0.717788)

t-Test: p = 0.2722 Wilcoxon Tests (Rank Sums): P = 0.2155

CHANGE IN EMOTIONAL By TREATMENT

Level	minimum	10.0%	Quantiles 25.0%	median	75.0%	90.0%	maximum
IL2-18kg	-6	-2.2	-1	1	3	5.4	8
IL2-9 kg	-9	-7	-3	-1	2	3.8	9

Means and Std Deviations				
Level	Number	Mean	Std Dev	Std Err Mean
IL2-18kg	27	1.10185	3.05263	0.58748
IL2-9 kg	31	-0.93548	4.35075	0.78142

Difference = 2.037 ~ 95% CI = (0.03160, 4.04307)

t-Test: p = 0.0466 Wilcoxon Tests: p = 0.0530

CHANGE IN FUNCTIONAL By TREATMENT

Level	minimum	10.0%	Quantiles 25.0%	median	75.0%	90.0%	maximum
IL2-18kg	-11	-6.17	-4	1	6.4	12.2	14
IL2-9 kg	-10	-6	-3.92	0.5	3	10.2	17

Means and Std Deviations				
Level	Number	Mean	Std Dev	Std Err Mean
IL2-18kg	27	1.50247	6.33581	1.2193
IL2-9 kg	32	0.63542	5.97942	1.0570

Difference = 0.867 95% CI = (-2.34827, 4.08237)

t-Test: p = 0.5913 Wilcoxon Tests: p = 0.5371

SUMMARY OF RESULTS

Most of the results in the previous pages pertain to study P410. The two groups of the study (dose 9 and 18) were fairly comparable with respect to all the demographic and medical characteristics we examine which included weight, total number of courses, total number of doses, age, and disease duration.

We examined percent changes from baseline in aquaphor, eucerin, pruritus visual analog scale, physician's global assessment, and calculated percent response value (page 9 - 10) None of the changes showed a significant difference between the two dose groups.

Duration of response from first dose (months) is provided on page 11. The median duration of 3.9 months for dose group of 9 and 4.6 months for the dose group of 18 was not found to be statistically significant.

Results of CTCL stage by dose administered are provided on page 12.

Documented response by DERC (**Data Endpoint** Review Committee) showed a total of **21** (29.6%) responders out of 71 patients (page 13). There were **8/35** ((22.9%) responders in the lower dose group and **13/36** (36.1%) responders in the higher dose group. The difference was not found to be significantly different (Fisher's Exact test: **p=0.30**). The documented response was defined as two tumor burden assessments over a period of at least six weeks.

Distribution by best response is also provided in a table on page 14. Similar profile of response was observed in the two groups.

Percent change from baseline in rescue medicine by documented response was also examined and median results are provided on pages 15-16. Except for percent change from baseline in eucerin use, all other changes were found to be significant between the two documented responses, implying that those who responded-did differ in the use of rescue medications.

We also received quality of life data for study **P410**. We evaluated change from baseline at visits 2, 3, and the follow-up visit (99). These results are provided on pages 17-22. Quality of life parameters we examined were physical wellbeing, social/family index, relationship with doctor, emotional behavior, and functional index. The treatment dose groups were not found to differ significantly for any of the mentioned parameters at any of the three examined visits.

Additional analyses of data from **P410** study were also conducted. The results are not included in this report but were provided to the medical reviewer.

CONCLUSION

Study **P401** was primarily a dose ranging study. On the basis of the results of this study, sponsor conducted study **P410** with two doses, 9 **mcg/kg/day** and 16 **mcg/kg/day**. Due to small number of patients per dose in **P401**, response data could not be evaluated.

Study **P410** is the primary randomized study. The two dose groups were found to be comparable with respect to baseline demographic and medical characteristics. The documented response rate in the higher dose was more than the response rate in the lower dose group; however, the rates were not found to be significantly different. There was an overall response rate of 29.6% in these patients. In general, the CTCL patients with the disease stage of 1 b to **IVa** do not expect to recover without a therapy. From the efficacy profile, both doses of the treatment were considered to be effective by the medical reviewers.